Functional Capsules via Subcomponent Self-Assembly

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CONSPECTUS: Coordination-driven self-assembly can produce large, symmetrical, hollow cages that are synthetically easy to access. The functions provided by these aesthetically attractive structures provide a driving force for their development, enabling practical applications. For instance, cages have provided new methods of molecular recognition, chirality sensing, separations, stabilization of reactive species, and catalysis.

We have fruitfully employed subcomponent self-assembly to prepare metal-organic capsules from simple building blocks *via* the simultaneous formation of dynamic coordinative (N→metal) and covalent (N═C) bonds. Design strategies employ multidentate pyridyl-imine ligands to define either the edges or the faces of polyhedral structures. Octahedral metal ions, such as Fe^{II}, Co^{II}, Ni^{II}, Zn^{II} and Cd^{II} constitute the vertices. The generality of this technique has enabled the preparation of capsules with diverse three-dimensional structures. This Account will highlight how fundamental investigations into the host-guest chemistry of capsules prepared through subcomponent self-assembly have led to the design of useful functions and new applications. We start by discussing simple host-guest systems, involving a single capsule, and continue to systems

that include multiple capsules and guests, whose interactions give rise to complex functional behavior.

Many of the capsules presented herein bind varied neutral guests, including aromatic or aliphatic molecules, biomolecules and fullerenes. Binding selectivity is influenced by solvent effects, weak noncovalent interactions between hosts and guests, and the size, shape, flexibility and degree of surface enclosure of the inner spaces of the capsules. Some hosts were able to adaptively rearrange structurally, or express a different ratio of cage diastereomers to optimize the guest binding ability of the system. In other cases the bound guest could be either protected from degradation or catalytically transformed through encapsulation.

Other capsules bind anions, most often in organic solvents and occasionally in water. Complexation is usually driven by a combination of electrostatic interactions, hydrogen bonding and coordination to additional metal centers. Anion binding can also induce cage diastereomeric reconfiguration in a similar manner to some neutral guests, illustrating the general ability of subcomponent self-assembled capsules to respond to stimuli due to their dynamic nature. Capsules have been developed as supramolecular extractants for the selective removal of anions from water, and as channels for transporting anions through planar lipid bilayers and into vesicles.

Different capsules may work together, allowing for functions more complex than those achievable within single host–guest systems. Incorporation of stimuli-responsive capsules into multi-cage systems allows individual capsules within the network to be addressed and may allow signals to be passed between network members. We first present strategies to achieve selective guest binding and controlled guest release using mixtures of capsules with varied affinities for guests and different stabilities towards external stimuli. We then discuss strategies to separate capsules with

encapsulated cargos *via* selective phase transfer, where the solvent affinities of capsules change as a result of anion exchange or post-assembly modification. The knowledge gained from these multi-cage systems may lead to the design of synthetic systems able to perform complex tasks in biomimetic fashion, paving the way for new supramolecular technologies to address practical problems.

1. INTRODUCTION

Subcomponent self-assembly is a powerful tool for the construction of diverse architectures that range from macrocycles, helicates, and polymers to metal-organic polyhedra and interlocked structures.[1] Its building blocks come together through the formation of coordinative (N→metal) and covalent (N═C) bonds, generating a substantial increase in structural complexity during a single self-assembly process. Metal-organic polyhedra have proven useful in applications that include recognition, chirality sensing, guest separation, stabilization of reactive species, and catalysis, *via* their well-defined inner spaces.[2-5] These abiological structures are also of relevance as functional mimics of biological molecules such as protein receptors and enzymes.[6]

This Account will focus on the functions of capsules prepared through subcomponent self-assembly in our laboratories over the course of the last five years. Work published prior to 2013 has been reviewed elsewhere together with the general design strategies for capsule contruction.[1] The functions of these structures result from the binding of neutral or anionic guests in their central cavities, giving rise to properties such as guest protection,[7] transformation,[8,9] extraction[10] and ion transport.[11] Variation of the subcomponents, counterions, or input of other chemical stimuli may also alter their properties, engendering complex behavior in multiple cage systems, such as selective guest binding and sequential guest release,[12-14] and transfer of cages between immiscible phases.[15,16]

2. ENCAPSULATION OF NEUTRAL GUESTS

Since our initial report of a capsule that was able to bind and stabilize pyrophoric white phosphorus, we have prepared a series of subcomponent self-assembled capsules that are able to bind aromatic and aliphatic compounds, biomolecules, and fullerenes within their central cavities. Several trends have emerged from these studies that shed light on the factors driving effective guest encapsulation in these systems. Choice of solvent strongly influences binding thus the selectivity can be tuned by altering the solubility of cages. The degree of surface enclosure is also crucial for effective guest binding with off-set or face-capping ligands being most effective at enclosing cavities. Large hydrophobic guests like fullerenes can be targeted by aromatic-paneled and porphyrin-based capsules. These host-guest systems can frequently reconfigure *via* cage structure conversion or altering their ratio of cage diastereomers to maximize the overall binding affinity of the system. Encapsulation can result in functions including protection of guests from degradation[7] and substrate transformation[8] within inner cavities.

2.1 Recognition of neutral guests

Solvophobic effects play an important role in the recognition of neutral guests in solution.[17] We have investigated solvent effects on guest binding through the preparation of cages that could be solubilized in more than one solvent, either through choice of counterion or *via* the use of differently substituted sub-components. For instance the sulfate salt of Fe_4L_4 tetrahedron **1** (Figure 1) was found to bind a wide variety of guests in water, while only a subset of these were bound by the triflate salt in acetonitrile, mainly aliphatic species.[18] This observation is consistent with recent findings that aromatic guests experienced a greater driving force for encapsulation in a metal-organic host in water than in acetonitrile, whereas aliphatic guests did not.[17] The subcomponent defining each face of **1** is flexible, allowing the cage to expand for larger or contract for smaller

guests. Moreover, large encapsulated guests, such as 2-hexylthiophene, reorganize to adopt coiled conformations that were thermodynamically disfavored in their free state. The chirotopic inner phase of the cage also rendered proton signals of chiral guests, such as *1R*-camphor, diastereotopic.

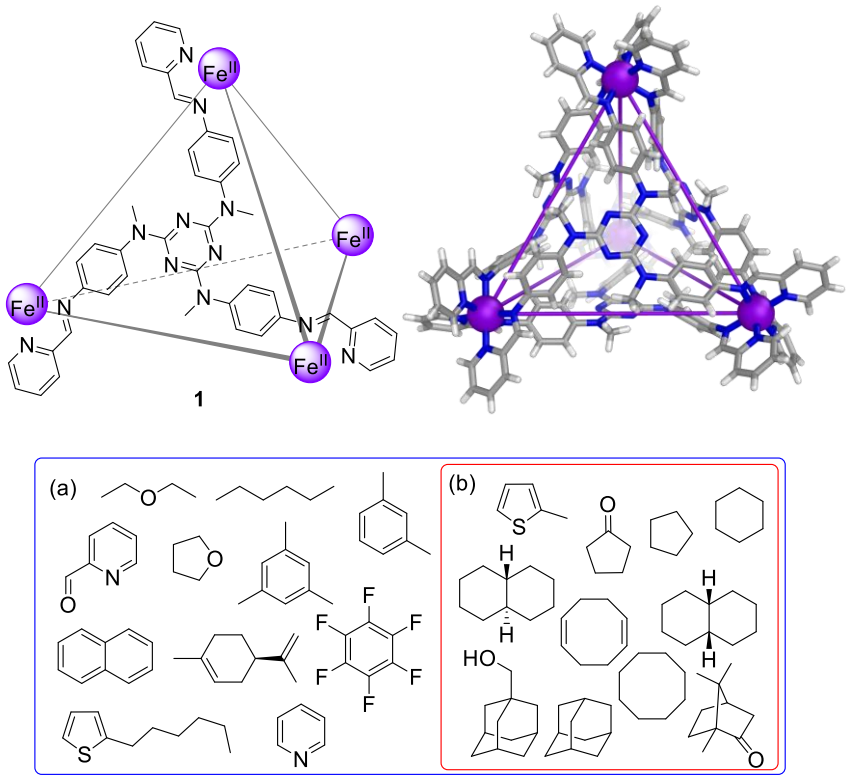

Figure 1. Structure of tetrahedron **1** and guests encapsulated. (a) In water all guests shown were encapsulated in **1**, whereas in acetonitrile only a subset (b) were encapsulated.

Solvent-dependent host-guest behavior was also exhibited by a Fe_8L_{12} cubic framework (Figure 2).[19] The geometry of 3,3'-diformyl-4,4'-bipyridine, together with 4-methylaniline and iron(II), gave rise to edge-bridged cubic cage **2**, which encapsulated ferrocene in acetonitrile. The alkyl chains of cube **3**, which incorporates 4-decylaniline residues, rendered it soluble in both acetonitrile and cyclohexane. Cube **3** encapsulated 9-acetylanthracene in cyclohexane but not in acetonitrile, which was attributed to enhanced dipolar and quadrupolar interactions in apolar cyclohexane.

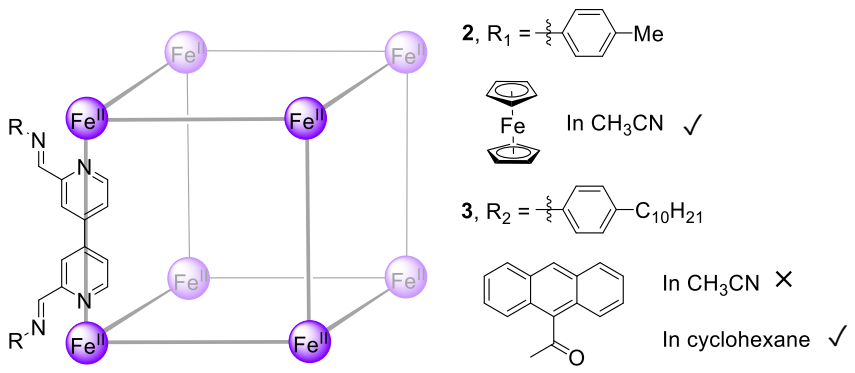

Figure 2. Structures of cubes **2** and **3** and guests encapsulated. In acetonitrile, **2** was able to bind ferrocene, while **3** encapsulated 9-acetylanthracene only in cyclohexane.

Similar behavior was also observed in a more enclosed porphyrin-faced Fe_8L_6 cube **4** (Figure 3). As the triflate salt, **4**-H_2 was able to bind large guests such as a fullerene or three molecules of coronene in DMF.[20] Anion metathesis with sulfate rendered **4**-H_2 and its hydrophobic cargo soluble in water.[21] Biologically relevant molecules, such as caffeine, inosine and steroids, were bound in water by porphyrinatozinc(II)-faced **4**-Zn. The hydrophobic effect appeared to enhance binding, as these cargoes bound only in water but not in acetonitrile.

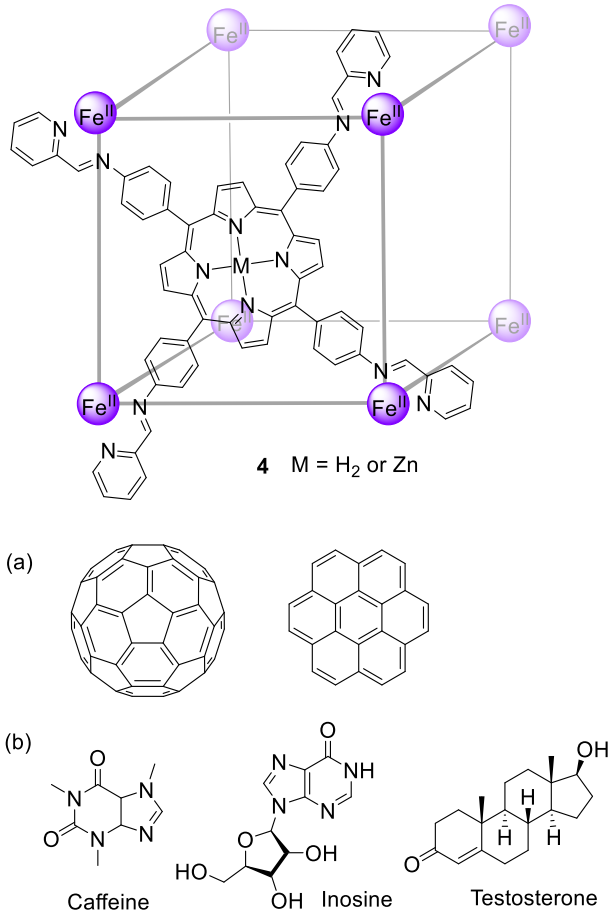

Figure 3. Structures of cubes **4**-H_2 and **4**-Zn. (a) Guests encapsulated by **4**-H_2 in DMF, and (b) guests encapsulated by **4**-Zn in water, but not in acetonitrile.

In addition to the solvent employed, the degree of cavity enclosure of a host has also been shown to strongly influence guest binding. A 1,6-pyrene-edged Fe_4L_6 tetrahedron **12** (Figure 4), which exists as a mixture of homochiral *T* (ΔΔΔΔ/ΛΛΛΛ), heterochiral C_3 (ΔΔΔΛ/ΛΛΛΔ), and achiral S_4 (ΔΔΛΛ) diastereomers, encapsulated natural products, such as cholesterol, in acetonitrile in fast exchange on the NMR timescale.[22] The polycyclic aromatic hydrocarbons perylene, pyrene and triphenylene also bound within **12** in fast exchange. Its large internal cavity allowed the cage to accommodate fullerenes C_{60} and C_{70} in slow exchange on the NMR timescale. In contrast to the

extensive binding properties of **12**, isomeric cage **6**, based on a more porous 2,7-pyrene scaffold, did not bind guests, indicating the importance of cavity enclosure for strong host-guest interactions.

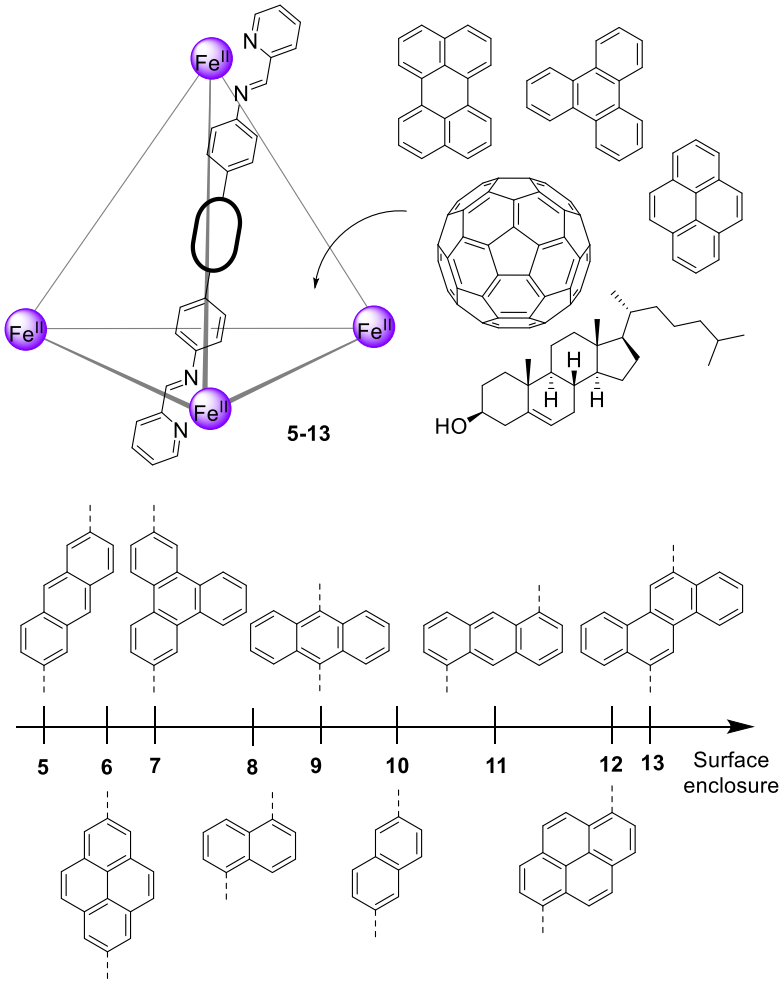

Figure 4. Structures of tetrahedra **5-13** with various aromatic spacers and guests investigated.

This enclosure principle was further demonstrated across a series of Fe_4L_6 cages **5-13** (Figure 4) containing aromatic panels of different sizes and geometries.[23] Offset aromatic spacers were observed to maximise the degree of surface enclosure, rendering the cavities suitable for binding large hydrophobic guests through aromatic stacking interactions. Through the series of cages subtle difference in the structure of subcomponents often resulted in incommensurate effects on the binding abilities of the resulting hosts. Following the binding of fullerenes, the three

diastereomers of cages **12** and **13** re-equilibrated, with amplification of the diastereomers best able to bind the guest in order to maximize the overall binding affinity of the system.

In addition to adaptation *via* diastereomeric reconfiguration, guest binding was also observed to induce cage to cage conversion. For example, upon addition of C_{60} to porphyrin-edged Fe_4L_6 tetrahedron **14** (Figure 5) in acetonitrile, the tetrahedron transformed into a new Fe_3L_4 host-guest complex C_{60}⊂**15**, adopting an arrangement that maximizes contact between porphyrin subunits and the fullerene guest.[24] The coordinative unsaturation of the apical Fe^{II} center of **15** also enabled the preparation of complex C_{60}⊂**16**, a heterometallic cone-shaped $CuFe_2L_4$ fullerene adduct that formed after addition of Cu^{I} and C_{60} to **14**.

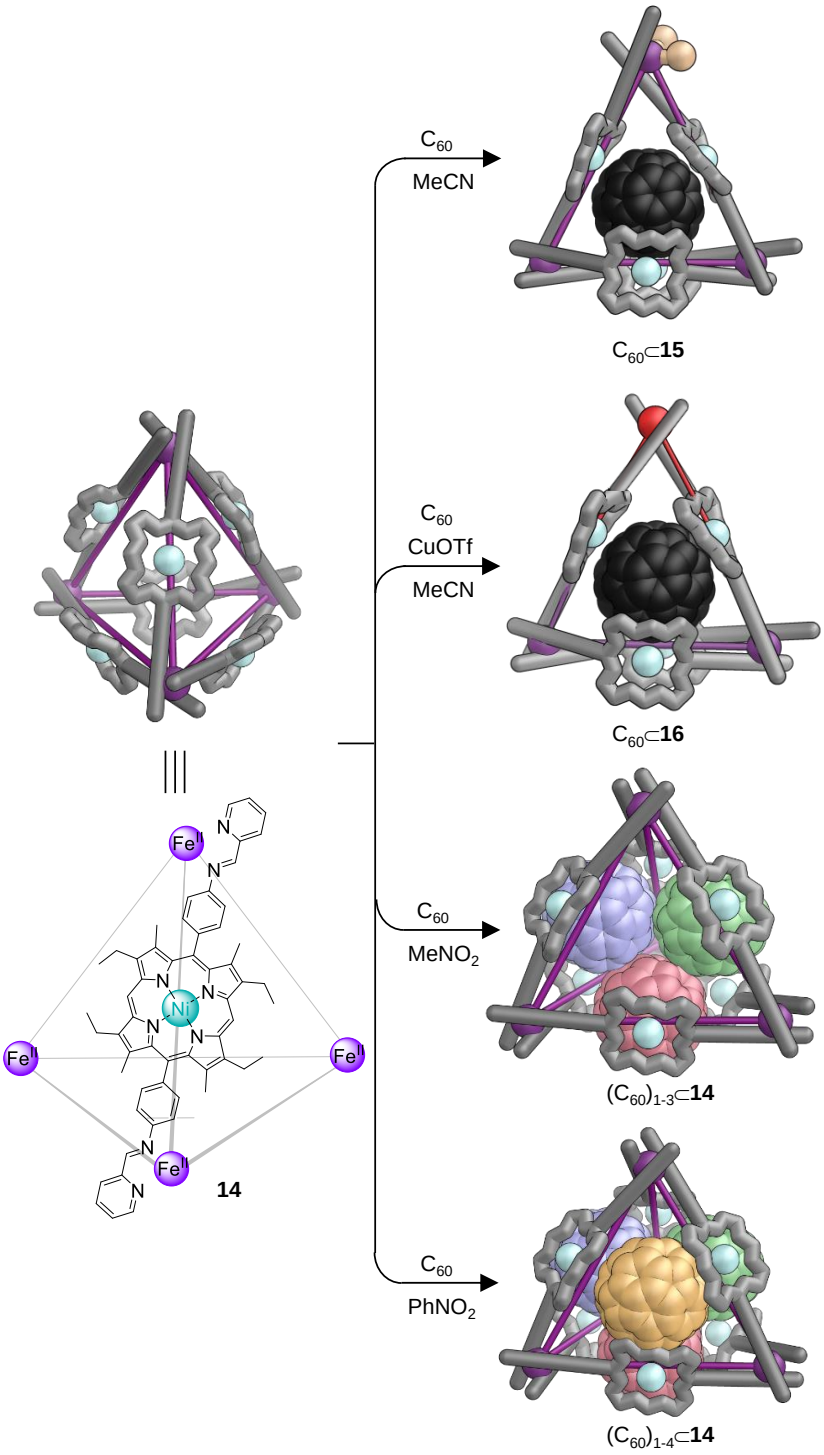

Figure 5. Structure of tetrahedron **14** and the solvent-dependent formation of fullerene adducts of **14-16**.

If the binding experiments were carried out in a less coordinating solvent nitromethane, binding of C_{60} by **14** resulted in the formation of a series of host-guest complexes containing 1-3 equiv of

C_{60} bound inside the cavity,[25] with no host framework rearrangement. The complex $(C_{60})_4$⊂**14** also formed when nitrobenzene was used as the solvent. These observations again emphasize the importance of solvent for the outcome of guest binding as discussed above. The molecules of C_{60} bound anticooperatively within well-defined pockets and the electron affinity of the overall cluster was increased by encapsulation.

Porphyrin-based $Co_{12}L_6$ cuboctahedron **17** (Figure 6) also encapsulated multiple fullerene guests, altering its stereochemistry to optimize host–guest interactions.[26] Cuboctahedron **17** was formed by the assembly of tetrakis(*p*-aminophenyl)porphyrin, 2-formylphenanthroline, and $Co(NTf_2)_2$ (Tf = CF_3SO_2). Incubation with excess C_{60} converted the initially *O*-symmetric **17** into S_6-symmetric host-guest complex $(C_{60})_2$⊂**18**. A third D_4-symmetric stereoisomer **19** formed when self-assembly occurred at room temperature; this isomer converted into *O*-symmetric **17** through heating or S_6-symmetric **18** through addition of fullerene guests. The assembly $(C_{60})_2$⊂**18** exhibited positive cooperativity in binding pairs of anionic guests around its periphery, whereas fullerene-free **17** bound the same anions with negative cooperativity.

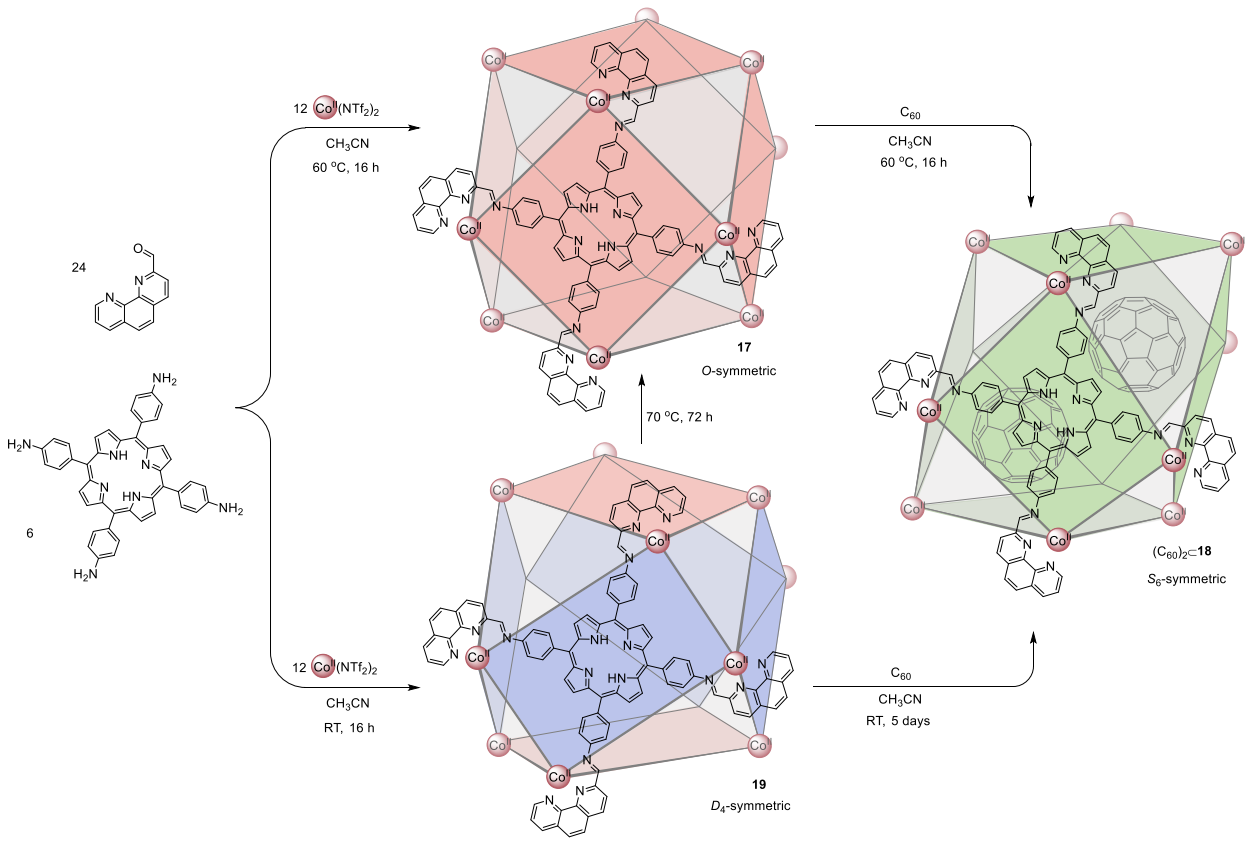

Figure 6. Self-assembly of **18** and **20** under different conditions, and formation of $(C_{60})_2$⊂**19**.

2.2 Protection of Guests by encapsulation

After demonstrating that a small tetrahedral capsule could be used as a supramolecular protecting group to stabilize white phosphorus[27] or to control a Diels-Alder reaction,[28] we were interested in extending this principle to larger, more complex guests. A large porphyrin-faced Fe_8L_6 cube **20** (Figure 7) was capable of protecting a peptide guest from degradation. Cube **20** exhibited binding properties towards biomolecules bearing imidazole motifs *via* coordination to its porphyrinatozinc(II) centers.[7] For instance, histidine-containing peptide **G1** was bound to **20** in a 2:1 stoichiometry. **G1** was efficiently protected from the degradation by protease trypsin in the presence of 0.6 equiv of **20**. In contrast, quantitative cleavage of non-binding peptide **G2**, which does not contain histidine, was observed in the presence or absence of **20**. Incubation of a mixture

of **G1**, **G2**, **20**, and trypsin thus resulted in the selective hydrolysis of **G2** with only 11% of **G1** hydrolyzed.

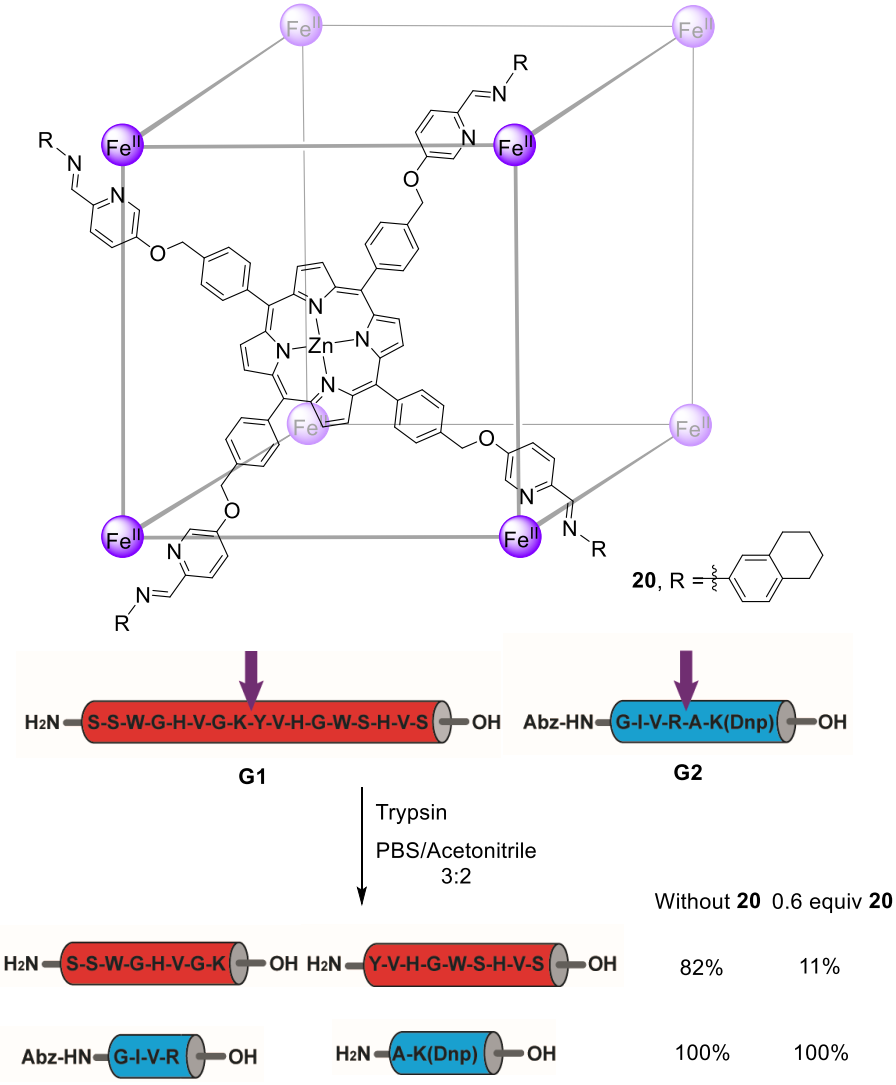

Figure 7. Trypsin treatment of peptides **G1** and **G2** in the presence of cube **20**. Arrows indicate the positions where the peptides are cleaved. Abz, 2-aminobenzoic acid; Dnp, 2,4-dinitrophenyl.

2.3 Transformation of encapsulated guests

In contrast to the protecting group strategy discussed above, the encapsulation of neutral guests may also lead to transformation of guests in certain cases. Water-soluble Fe_4L_6 tetrahedra ΔΔΔΔ-

21 and ΛΛΛΛ-**21** (Figure 8a) were prepared in enantiopure form, with the handedness of the cage framework being determined by the chirality of their glyceryl substituents. These cages bound many hydrophobic guests in water.[8] Enantiopure ΔΔΔΔ-**21** interacted differentially with the two enantiomers of limonene, thus acting as an encapsulative chiral-shift reagent. The organophosphate pesticide dichlorvos was found to bind strongly in fast exchange on the NMR timescale. The presence of 1 mol% of ΔΔΔΔ-**21** resulted in the catalytic hydrolysis of dichlorvos to less toxic compounds (Figure 8b), dimethyl phosphoric acid (DMP) and dichlorovinylmethyl phosphoric acid (DVMP).

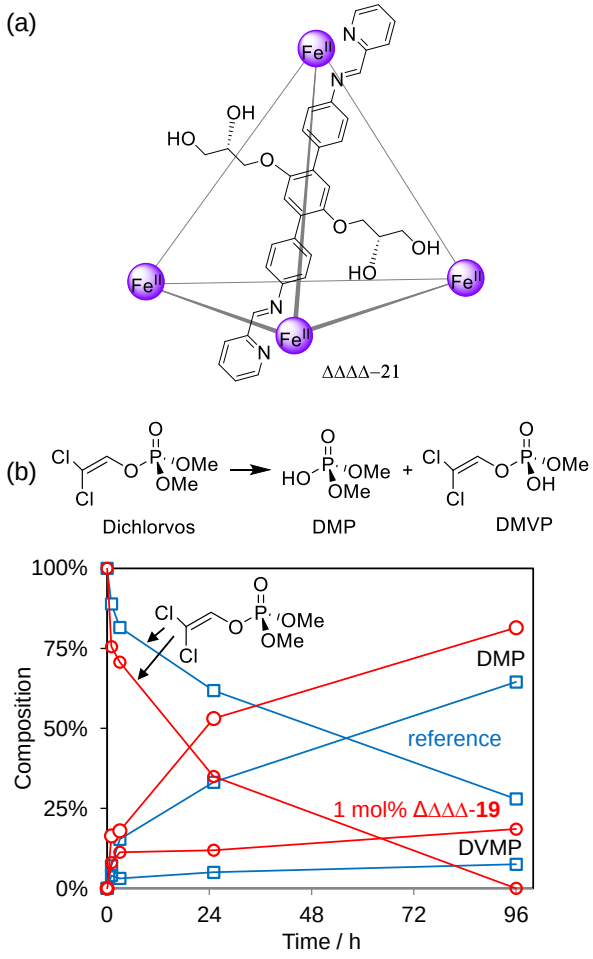

Figure 8. (a) Structure of ΔΔΔΔ-**21**, and (b) hydrolysis of dichlorvos in 0.1 mM phosphate buffer at pH 7 and 298 K in the absence and presence of ΔΔΔΔ-**21**.

As well as achieving a one-step catalytic process, we also incorporated an Fe_4L_6 tetrahedron **22** into a multistep catalytic transformation of several simple substrates into a more complex product (Figure 9).[9] Initially the aqueous mixture contained the subcomponents necessary to assemble **22**[29] together with furan, nitromethane, *L*-proline, methylene blue, and dioxygen. The photosensitizer methylene blue first generated singlet oxygen, which then underwent hetero-DA cycloaddition with furan to produce a high-energy endoperoxide intermediate (cycle A). Concurrently, tetrahedron **22** assembled and catalyzed the transformation of the endoperoxide into **b**, which was not observed in the absence of **22** (cycle B). Intermediate **b** in turn fed into cycle C to afford the final product **c** in 30% overall yield through catalysis by *L*-proline. The absence of any components of the cage led to nonselective pathways, whereby the endoperoxide reacted to give different products. Key features of this system are the *in situ* self-assembly of **22** and the lack of interference between the different catalytic cycles.

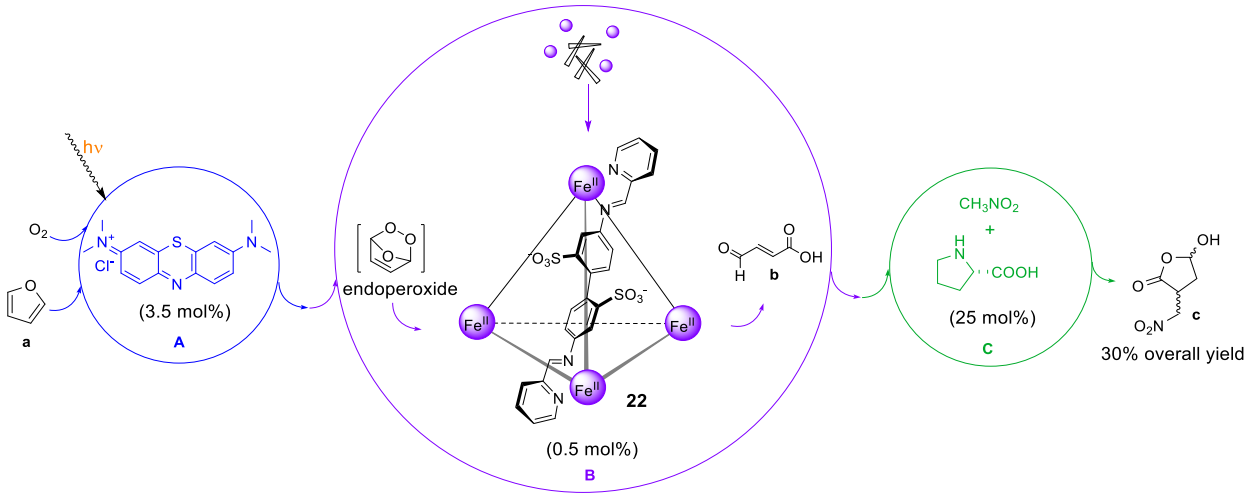

Figure 9. Relay multicatalytic system, in which all steps take place in water at room temperature.

3. ENCAPSULATION OF ANIONS

Anion complexation by synthetic molecular receptors is an important area of supramolecular chemistry due to the environmental and biological significance of these guests.[30] The positively

charged nature of the majority of subcomponent self-assembled capsules make them attractive candidates for the recognition of anions *via* electrostatic interactions. In some cases binding could also be enhanced through hydrogen bonding interactions or coordination to additional metal ions in the structure. In most cases these anion binding events have been studied in organic solvents. Anion binding in water has been achieved less frequently due to the high hydration energy of the anions and the instability of many capsules in water, as a consequence of the hydrolysis of imine bonds and the low water solubility of many subcomponents. As observed for neutral guest encapsulation, anion binding could also induce cage diastereomeric reconfiguration to express the diastereomers with the highest guest binding affinities. In other cases strongly binding anions, sometimes formed *in situ*, could act as templates to direct the subcomponents to form a structure that did not form in their absence. High affinity of anion binding is also relevant in the context of designing supramolecular extractants for chemical purification.[10] Metal-organic assemblies can also act as ion channels, capable of transporting anions through planar lipid bilayers and into vesicles.[11]

3.1 Recognition of anions

Biphenyl-edged Fe_4L_6 tetrahedron **23** was found to exist as a mixture of homochiral *T* (ΔΔΔΔ/ΛΛΛΛ), heterochiral C_3 (ΔΔΔΛ/ΛΛΛΔ), and achiral S_4 (ΔΔΛΛ) diastereomers in acetonitrile, in a similar manner to edge-bridged cage **12** (Figure 10).[31] Upon addition of one of the anions Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, BF_4^-, or PF_6^-, the system reconfigured by expressing a set of diastereomers that optimized binding of the anionic guest, as observed in the case of fullerene binding by **12**. Not only did the cage diastereomers interconvert, the volume of the individual cages also adapted through bond rotation in order to optimize guest binding through non-classical hydrogen bonding interactions.

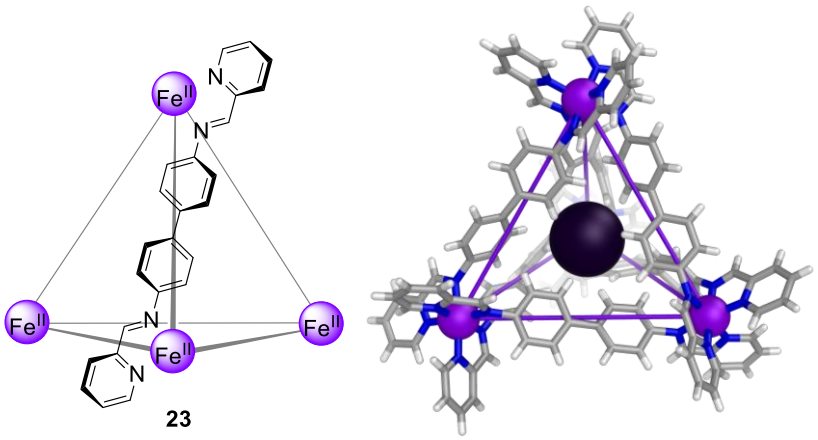

Figure 10. Structure of tetrahedron **23** and its X-ray crystal structure with a bound I^- anion.

Due to their strong binding affinity, anions also frequently serve as templates for the formation of metal-organic capsules.[32] In the system shown in Figure 11, both the anionic template and the cage were mutually stabilized through complex formation.[33] In the absence of KBr, Co_4L_6 tetrahedron **24** did not form in acetonitrile. After addition of KBr, a metallate anionic guest and the capsule were formed together *in situ* as the species $CoBr_4^{2-}\subset$**24**, with the four bromine atoms of the guest pointing out of the faces of the tetrahedron. This concept was further extended in the preparation of other $CoX_4^{2-}\subset Co_4L_6$ or $ZnX_4^{2-}\subset Zn_4L_6$ complexes (X = Cl^-, I^-, OCN^-, SCN^-).

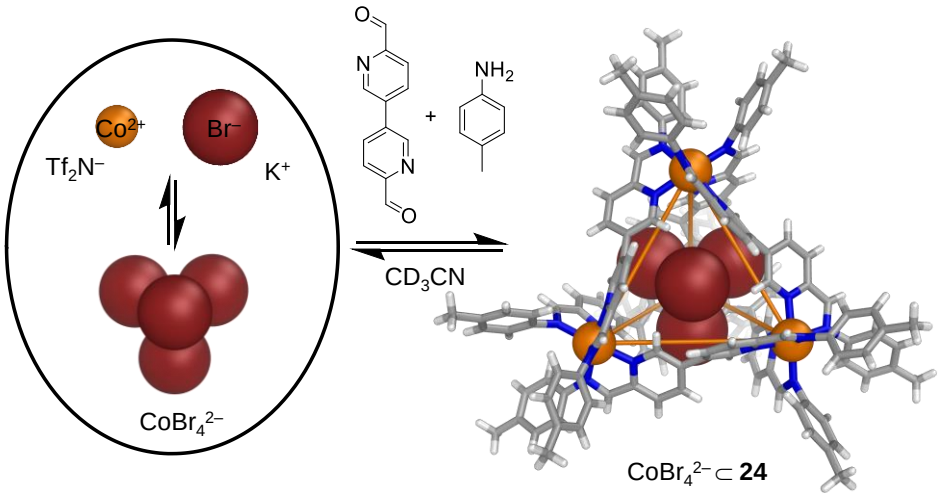

Figure 11. Formation of $CoBr_4^{2-}\subset$**24** driven by the *in situ* formed $CoBr_4^{2-}$ anionic template.

Other guest species such as CO_3^{2-} or SO_4^{2-} could be trapped out of equilibria resulting from dissolved CO_2 or SO_2. The self-assembly of a bent dialdehyde subcomponent with 4-methoxyaniline and $Cd(OTf)_2$ or $Zn(BF_4)_2$ led to the formation of M_5L_6 trigonal bipyramidal structures **25** or **26**, containing two apical and three equatorial metal ions (Figure 12).[34] The X-ray structure of **25** revealed a CO_3^{2-} anion, arising from the atmospheric CO_2, coordinated to the three equatorial cadmium centers in addition to two TfO^- anions occupying binding pockets in the structure. Exposure of the zinc analog **26**, initially formed under a N_2 atmosphere, to air also led to the formation of its CO_3^{2-} adduct. SO_2 was also bound to **26** as SO_3^{2-}, followed by oxidation to give bound SO_4^{2}.

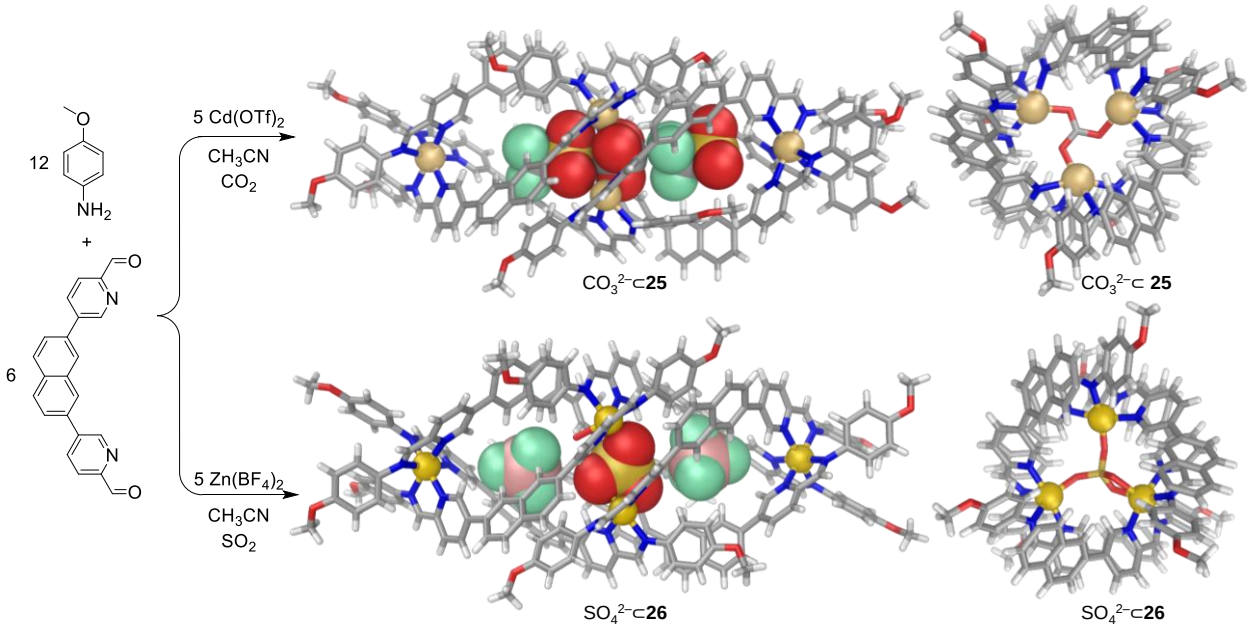

Figure 12. X-ray structures of $CO_3^{2-}\subset$**25** and $SO_4^{2-}\subset$**26**, and their formation *via* subcomponent self-assembly.

Although large self-assembled capsules are frequently too porous for efficient guest binding, face-capped cube **27**, having a diameter of ca. 5 nm, was capable of binding large anions that included $Mo_6O_{19}^{2-}$, $B_{12}F_{12}^{2-}$, BPh_4^-, $CB_{11}H_{12}^-$, and $B(C_6F_5)_4^-$ in acetonitrile (Figure 13).[35] The smaller but more porous cube **28** did not bind anions. The crystal structure of **27** indicated that the

anthracenyl groups mostly lie parallel to the cube faces, creating an enclosed cavity with a volume greater than 4200 Å^3. Cavity enclosure and coulombic effects thus appeared to be crucial factors for binding, while the degree of cavity occupancy was less important.

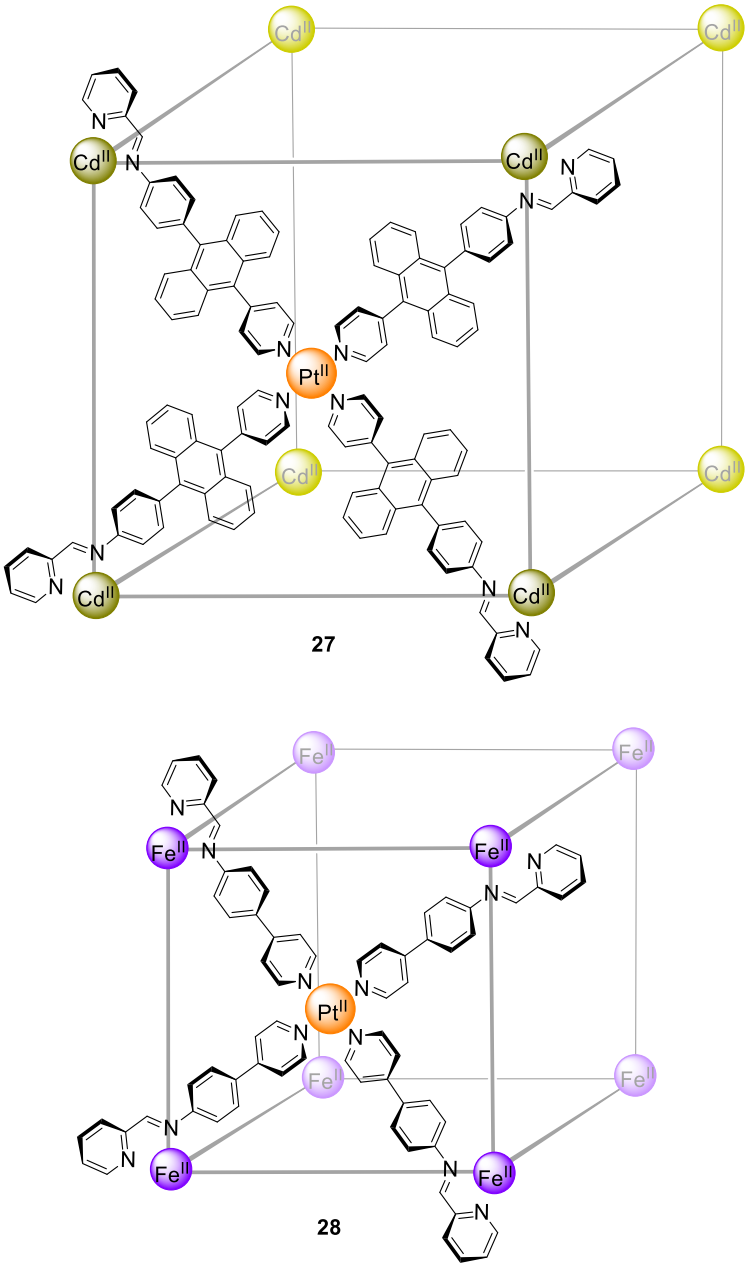

Figure 13. Structures of **27** and **28**.

Another heterometallic cube **29**, containing molybdenum(II) paddlewheel faces, bound different anionic guests in acetonitrile (Figure 14).[36] The coordinatively unsaturated molybdenum centers served as binding sites for halides. A hierarchy of halide binding was observed ($I^- > Br^- > Cl^- > F^-$), consistent with the preference of the molybdenum centers for softer, more polarizable ligands. The zinc(II)-cornered analog **30** exhibited the same binding order. Incorporation of fluorine substituents inverted the halide binding preference of Zn^{II} cube **32** due to perturbation of the dynamic behavior of the ligand and the electronics of the molybdenum sites, whereas Fe^{II} cube **31** maintained a similar binding hierarchy to its non-fluorinated congener.[37] This phenomenon indicated that subtle ligand modifications led to significant variations in guest binding properties.

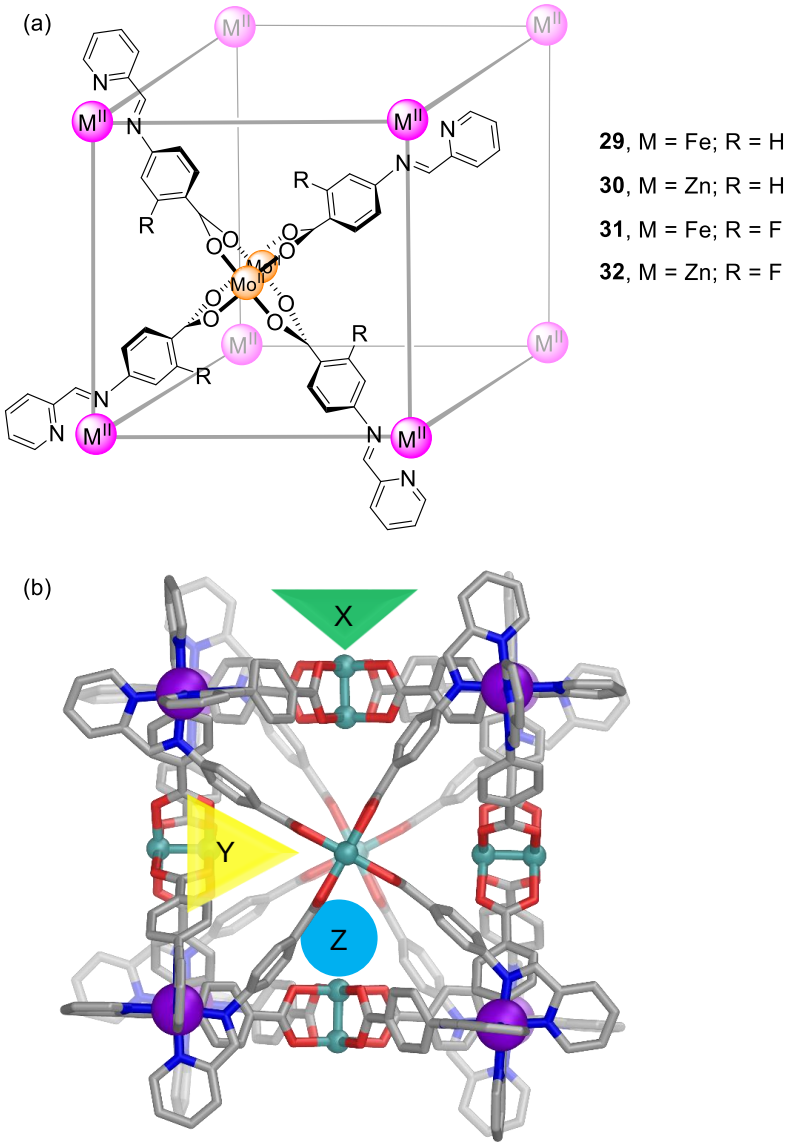

Figure 14. (a) Structures of **29**-**32**, and (b) X-ray crystal structure of **29**, showing the external allosteric regulation sites (X and Y) of the internally bound guest (Z).

Other coordinating species, NH_3, $OPMe_3$, and $CF_3CO_2^-$, could also bind inside **29** and influence the further uptake of iodide, showing an allosteric influence.[36] In addition, there were two further allosteric regulation sites (X and Y in Figure 14b) that modulated the internal binding of guest (Z) within **29**.[38] The ligation of neutral coordinating species, such as trialkylphosphines, to exterior binding sites (X) inhibited the internal binding of I^- or $Mo_2O_7^{2-}$ within **29**. Clefts in the architecture of **29** created a second type of allosteric site, Y, able to bind BPh_4^-, which inhibited the

encapsulation of I^- or $Mo_2O_7^{2-}$. The two individual allosteric sites influenced internal binding independently.

Pseudo-octahedral M_6L_4 capsules **33-36** also possess two individual binding sites, for peripheral and internal anions encapsulation in acetonitrile (Figure 15).[39] Tetraphenylborate derivatives ($B(C_6H_5)_4^-$, $B(C_6H_4F)_4^-$ and $B(C_6H_4Cl)_4^-$) were found to bind externally to **33-35**, with one phenyl ring pointing into the cavity, whereas $CB_{11}H_{12}^-$, PF_6^-, AsF_6^- and SbF_6^- were encapsulated centrally. No allosteric effect was observed in this case: the binding of an anion in one site did not affect the anion binding strength at the other site. Interestingly, **36** could only be prepared using $B(C_6H_5)_4^-$ as a peripheral template. Once formed, the capsule bound guests in its central cavity.

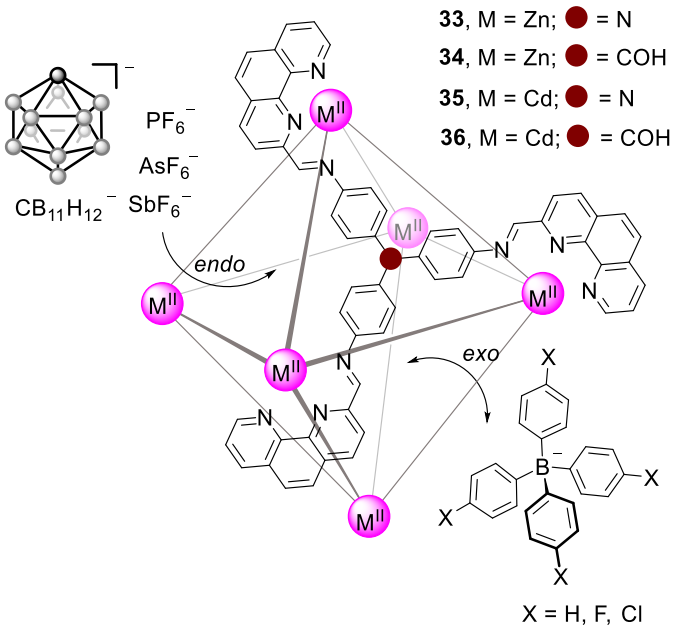

Figure 15. Structures of **33-36** and their *exo*- and *endo*-bound anionic guests.

3.2 Anion extraction

Anion extraction is an important practical application of anion recognition. We recently reported the formation of endohedrally functionalized Fe_4L_4 tetrahedron **37** (Figure 16) from an

azaphosphatrane subcomponent, which was able to encapsulate various template anions in water *via* hydrogen bonding and electrostatic interactions.[40] Competitive guest exchange studies suggested a preference for ReO_4^- binding in water over other anions, indicating the potential of **37** as an extractant of this anion from water. Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAr_F^-) was then chosen as the counterion of the capsule, so that **37** became soluble in the water-immiscible organic solvent, nitromethane.[10] *N*-butyltrifluoroborate-templated $^n BuBF_3^-$⊂**37** was used as a supramolecular extractant, which was able to extract an equimolar amount of ReO_4^- from water into nitromethane to displace $^n BuBF_3^-$ forming ReO_4^-⊂**37**. The extraction proceeded selectively even in the presence of 10 other competing anions. Moreover, by switching the solvent from nitromethane to ethyl acetate, the extracted ReO_4^- could be released into water as the cage disassembled in ethyl acetate layer. Addition of acetonitrile and $^n BuBF_3^-$ after evaporation of ethyl acetate then brought about regeneration of cage $^n BuBF_3^-$⊂**37**.

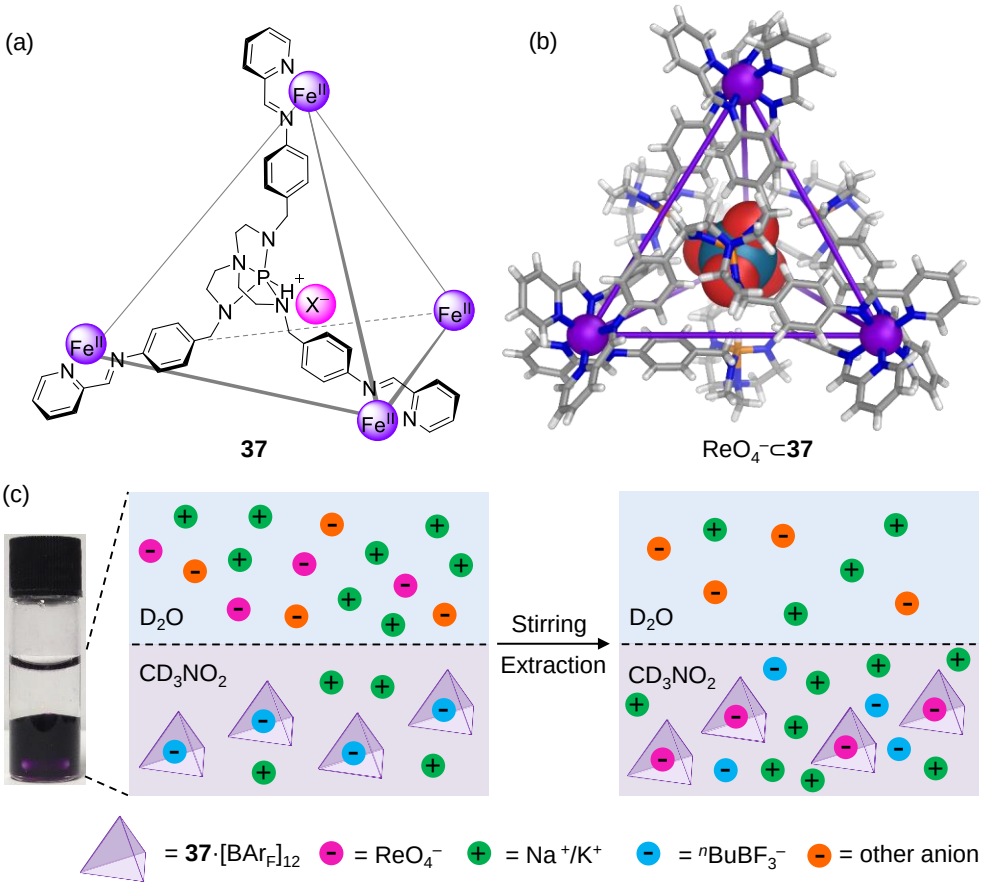

Figure 16. (a) Structure of X^{-}⊂**37**, (b) X-ray crystal structure of ReO_4^{-}⊂**37**, and (c) selective liquid-liquid extraction of ReO_4^{-} by **37**, in the presence of other competing anions.

3.3 Cages as ion channels

Another practical application of anion binding is anion transport. Peripheral functionalization of $Zn_{10}L_{15}$ pentagonal-prism **38**[33] generated a new complex **39** that is able to insert into lipid bilayers to act as synthetic ion channels (Figure 17).[11] Architecture **38** was templated by five perchlorate anions within peripheral binding pockets, and a sixth halide anion located in the central, channel-like cavity. The long alkyl chains of new complex **39** were designed to enhance its lipophilicity and dimensions to match the thickness of a lipid bilayer. Ionic current measurements indicated the successful insertion of **39** into planar lipid bilayers, and an HPTS fluorescence assay demonstrated

transport of ions across the membrane. Halide ions were selectively transported by **39** over larger anions like NO_3^-, SO_4^{2-} and ClO_4^-. The transport of Cl^- into vesicles was also demonstrated. In membranes, dodecyl sulfate was able to plug into the central channel of **39**, blocking chloride transport.

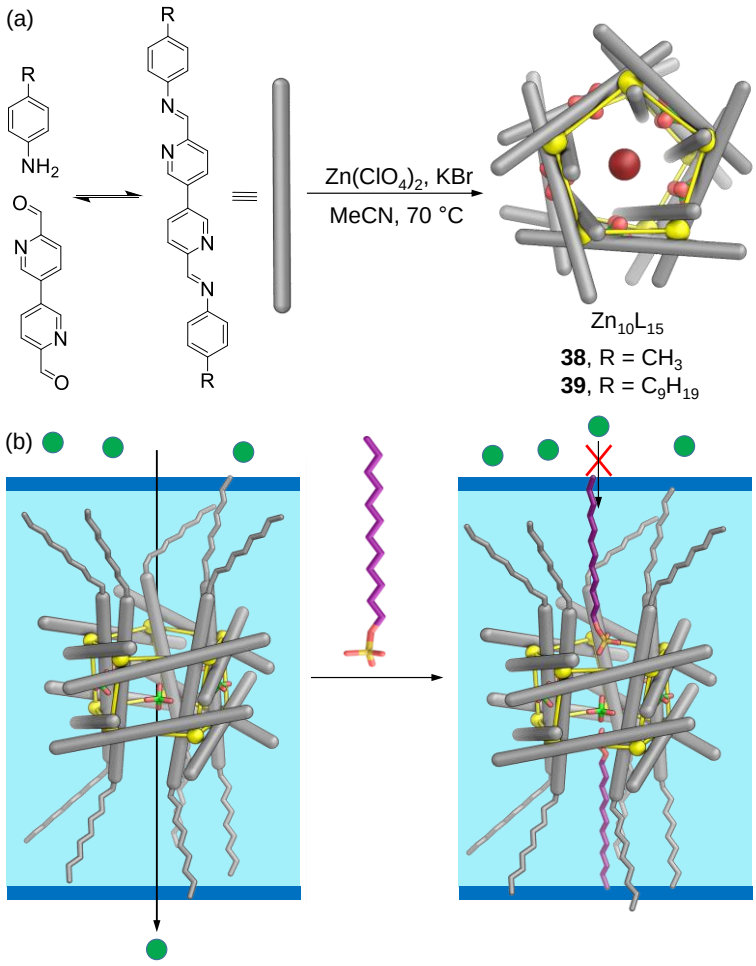

Figure 17. (a) Self-assembly of **38** and **39** and (b) schematic representation of anion transport through the channel of **39** across a membrane and its blocking by dodecyl sulfate. Equatorial chains of **39** have been omitted for clarity.

4. COMPLEX SYSTEMS INCORPORATING MULTIPLE CAGES

Complex chemical behavior is a feature of living organisms. Biological systems consist of mixtures of molecules that self-organize into networks, functioning cooperatively to achieve goals

that they cannot achieve individually. The emerging field of systems chemistry provides tools to design synthetic networks to perform complex functions.[41] In contrast to the simple systems involving a single capsule discussed above, this section will focus on systems comprised of a collection of host and guest molecules. When exposed to external stimuli, a member of the system will respond and affect other members, allowing signals to propagate through the network and complex functions to emerge. Based on the fundamental host-guest investigations discussed above, we were able to design several systems of cages that show selective guest binding and sequential guest release in response to external stimuli,[12-14] and separate cages together with their cargos by phase transfer strategies.[15,16]

4.1 Selective guest binding and sequential guest release

The self-sorting synthesis, selective encapsulation, and sequential guest release in a system of three metal-organic hosts has been demonstrated (Figure 18).[12] A mixture of two triamines, one diamine, 2-formylpyridine and a Zn^{II} salt was found to self-sort, producing a mixture of three tetrahedra **40-42** in acetonitrile, with each encapsulating a different guest. Differences in stability among capsules **41** and **42** allowed their guests to be released in a specific sequence following the addition of 4-methoxyaniline, which sequentially reacted with **42** and then **41**, opening each in turn and releasing its guest. Cage **40** remained intact until heating brought about reaction with 4-methoxyaniline and liberation of its guest.

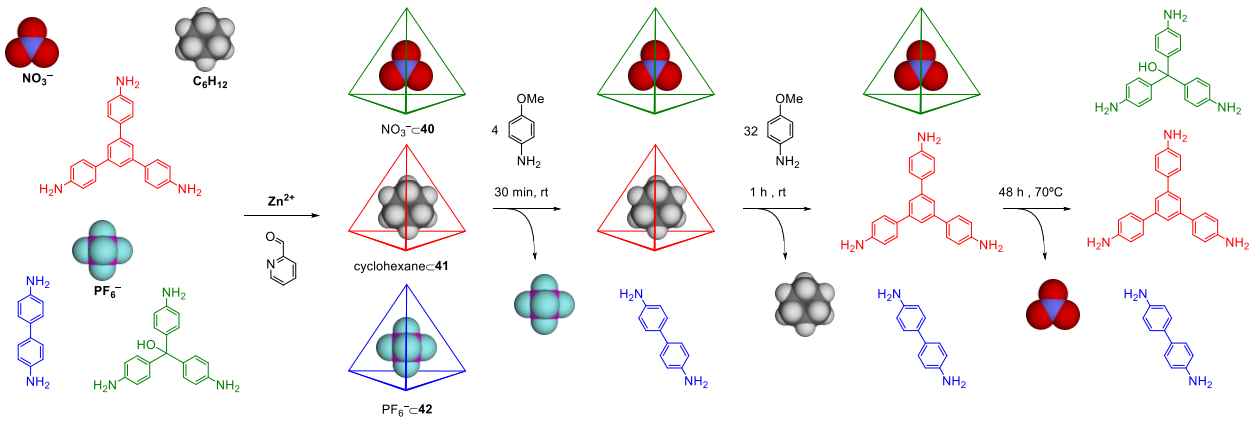

Figure 18. One-pot self-sorting system of encapsulation and release of the guests from cages **40**-**42**.

Zn_4L_4 capsules **41** and **43** exhibited sequence-dependent guest release behavior in response to the order of two distinct chemical stimuli (Figure 19).[13] Two different neutral guests, cyclohexane and chloroform, were selectively encapsulated in hosts **41** and **43**, respectively. In sequence I, addition of 4 equiv of tris(2-aminoethyl)amine (tren) to the system led to selective release of cyclohexane upon the disassembly of **41**. Subsequent addition of ReO_4^- brought about the complete displacement of $CHCl_3$ from the cavity of **43** owing to its stronger binding affinity. The ReO_4^- was released following the addition of a further 4 equiv of tren to the system, which resulted in the conversion of **43** into insoluble polymeric products.

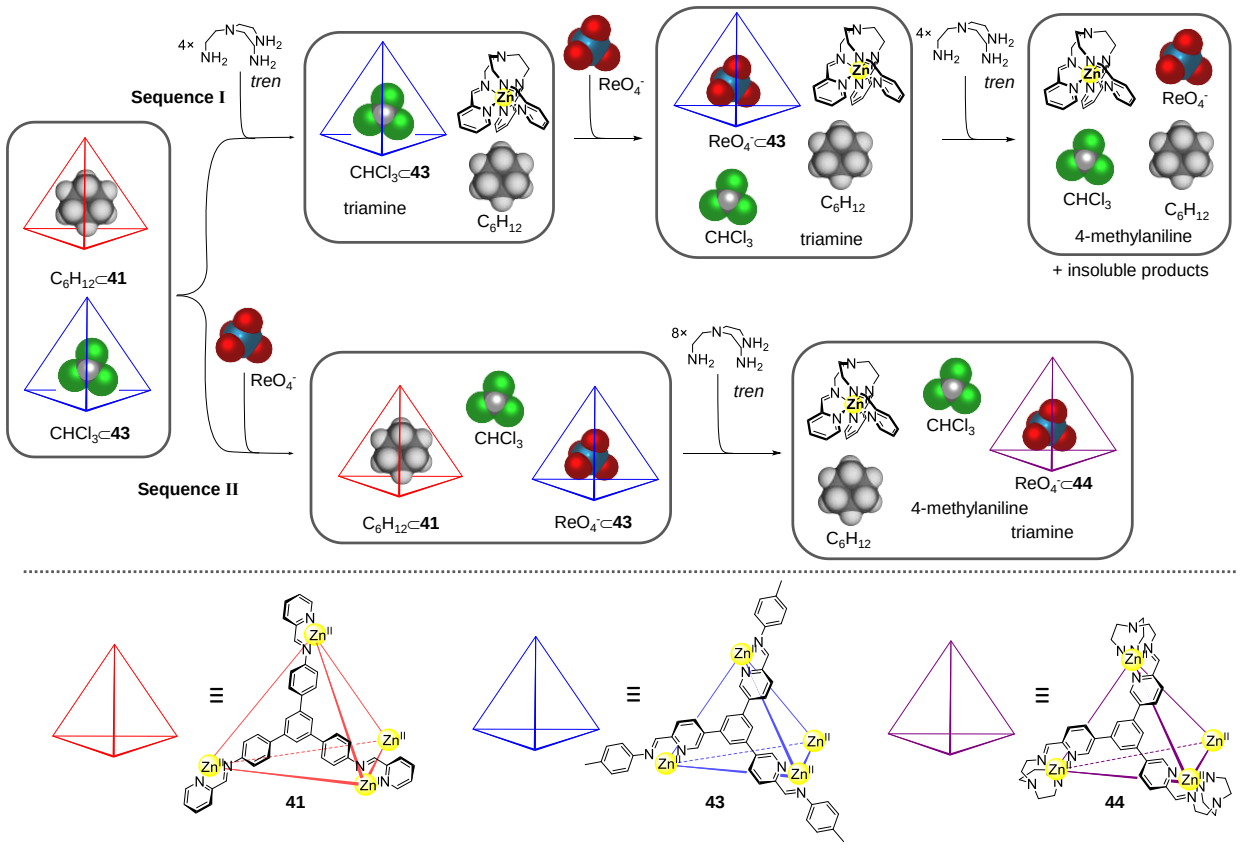

Figure 19. Sequence-selective release of guests triggered by orthogonal chemical signals.

When the order of applied signals was reversed in sequence II, initial displacement of the $CHCl_3$ from **43** by ReO_4^- was followed by a different outcome when 8 equiv of tren were subsequently added. These conditions suppressed the formation of polymeric products, instead resulting in the conversion of **43** into **44**, which retained ReO_4^-.

The differential stabilities of high-spin and low-spin analogs of a Fe^{II} tetrahedral capsule were also used for selective guest release in a two-cage system (Figure 20).[14] Upon addition of 4-methoxyaniline to a mixture of **45** and **23**, which encapsulate 1-fluoroadamantane (1-FA) and BF_4^- respectively, high-spin **45** reacted with 4-methoxyaniline preferentially, releasing its 1-FA guest. In contrast, the transformation of high-spin **45** to low-spin **1** through exchange of the aldehyde residues from 2-formyl-6-methylpyridine to 2-formylpyridine, rendered the face-capped capsule

more stable than edge-bridged low-spin **23**. Thus the addition of 4-methoxyaniline resulted in selective disassembly of **23**, releasing its BF_4^- guest.

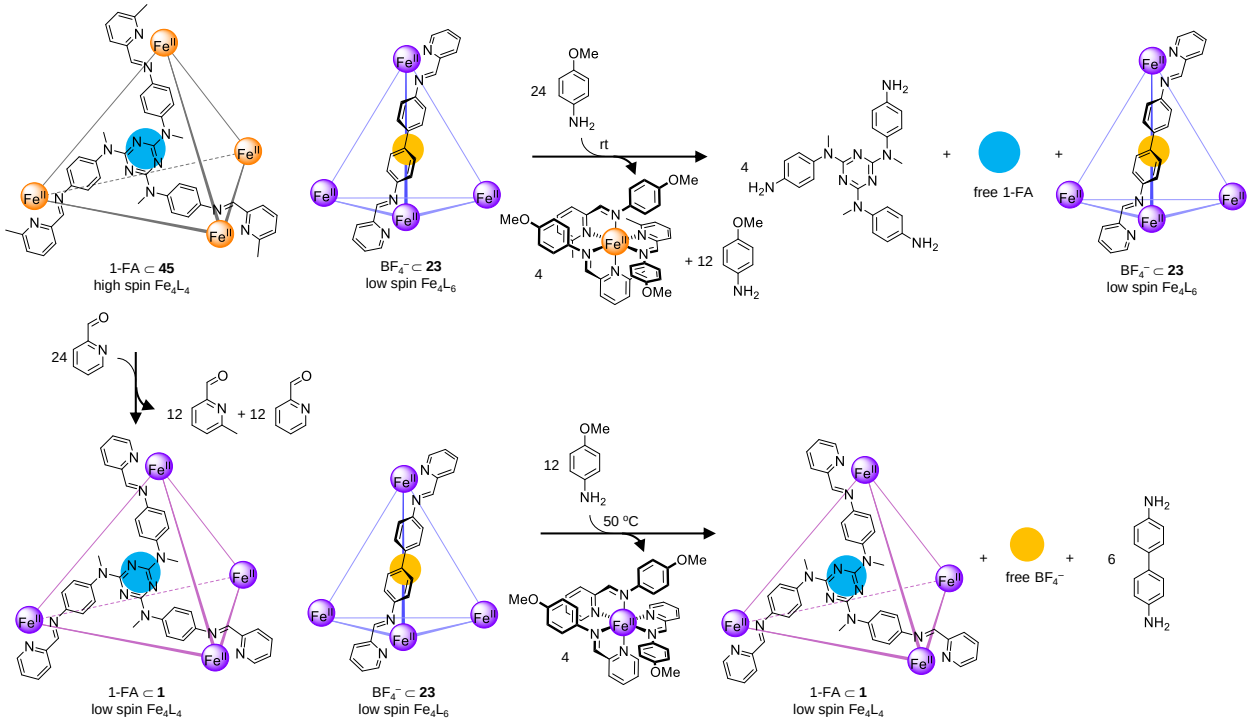

Figure 20. Different outcomes of selective cage disassembly and guest release triggered by 4-methoxyaniline, before and after the reaction of high-spin **45** with 2-formylpyridine.

4.2 Separation of capsules by phase transfer

Phase transfer, in which a capsule and its cargo transit from one phase to another across a phase boundary, is a means of separating capsules together with their guests. This approach may ultimately allow the separation of industrially relevant compounds.

An initial study showed that three different metal-organic cages with guests preferentially dissolved in three different phases, water and two other mutually immiscible hydrophobic ionic liquids (ILs).[42] Following the initial results, we demonstrated that Fe_4L_4 tetrahedron **46** (Figure 21) was able to transport a cargo, 1-FA, from water into a hydrophobic ionic liquid layer, 1-ethyl-3-

methylimidazolium triflimide ([emim][NTf_2]), triggered by an anion exchange from SO_4^{2-} to Tf_2N^- after mixing the two phases.[15] Separation of the mixture of **46** and **22** and their respective encapsulated cargos was achieved by mixing their aqueous solution with [emim][NTf_2], which resulted in the selective phase transfer of cationic cage **46** into the IL layer, whereas anionic cage **22** remained water-soluble.

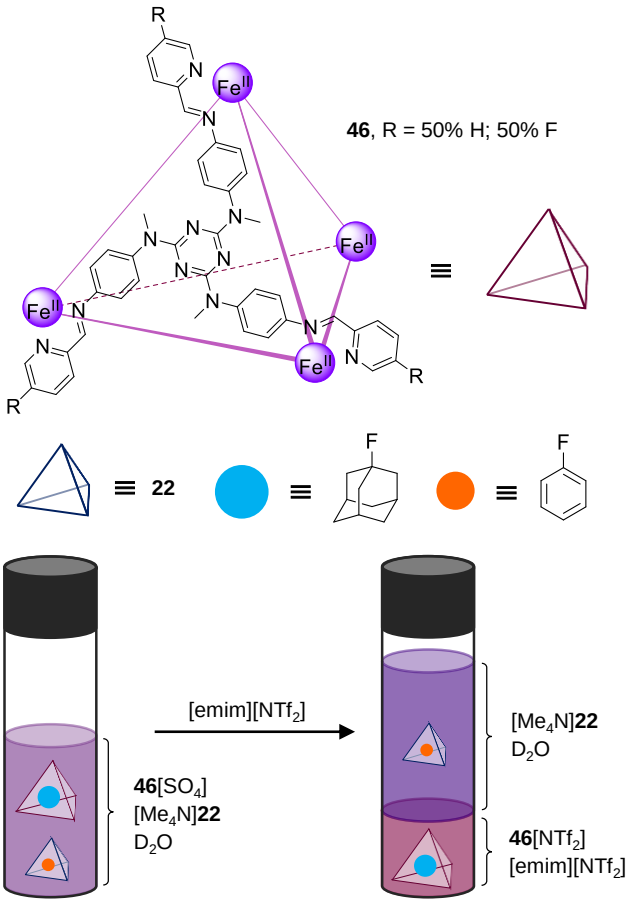

Figure 21. Selective phase transfer of cage **46** and its encapsulated cargo.

Selective phase transfer also allowed the separation of two capsules obtained by a post-assembly modification (PAM) cascade.[16] An equimolar mixture of tetrazine-edged Fe_8L_{12} cube **47** and maleimide-functionalized Fe_4L_6 tetrahedron **48** (Figure 22) underwent a tandem sequence of inverse-electron-demand Diels-Alder (IEDDA) and normal electron-demand DA reactions

connected *via* a transient relay signal. The cascade was initiated by 2-octadecylnorbornadiene, which underwent IEDDA reactions with the tetrazines of **47** to give pyridazine-edged cube **48** and an 1-octadecylcyclopentadiene (C_{18}-CPD) intermediate. C_{18}-CPD subsequently reacted with the maleimides of **48**, generating the C_{18}-norbornene moieties of tetrahedron **50**. The alkyl chains of **50** rendered it sufficiently lipophilic to cross a phase boundary from more polar acetonitrile to non-polar cyclopentane, thus isolating it from **49**.

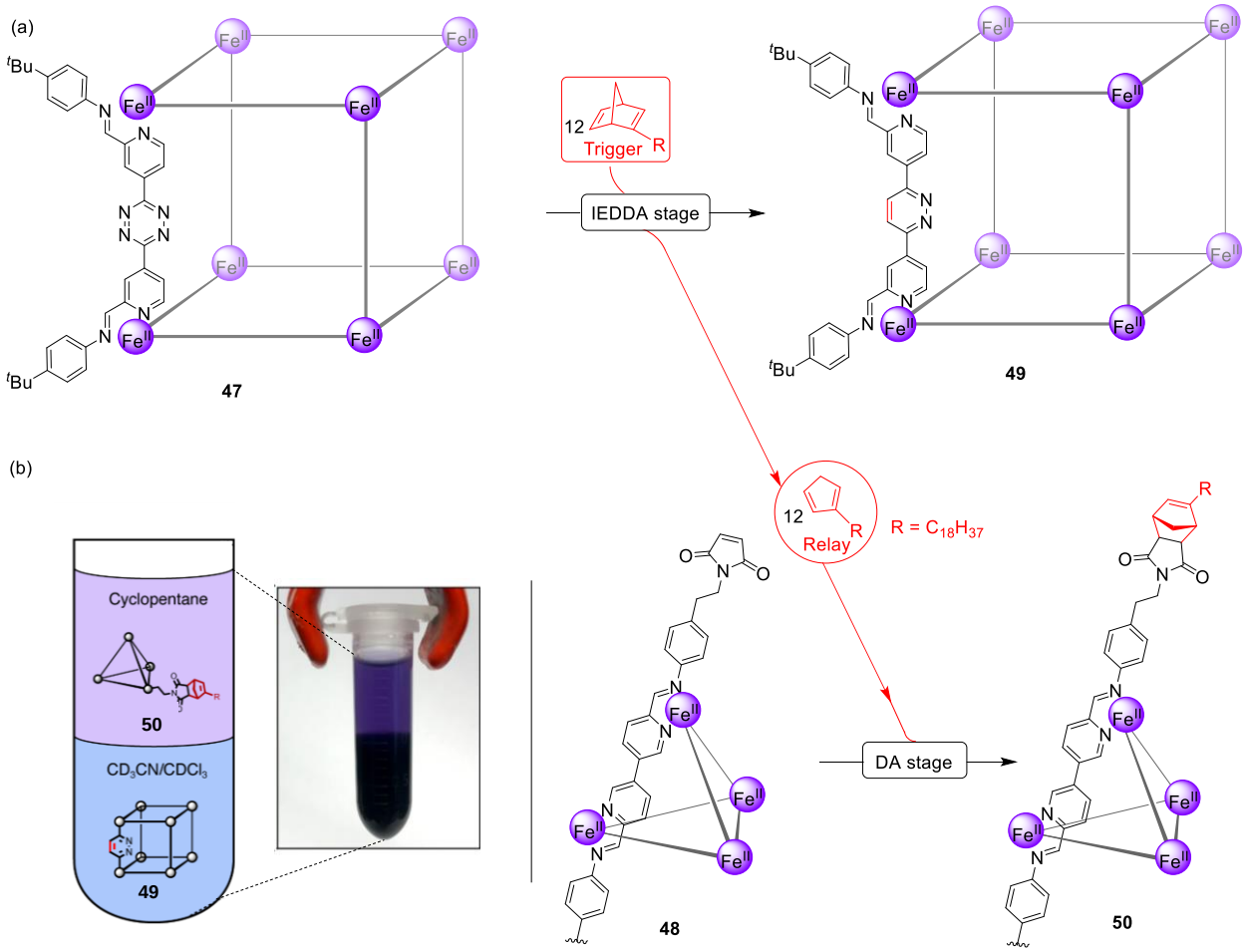

Figure 22. (a) Structures of **47**-**50** and the PAM cascade, and (b) separation of **49** and **50** by phase transfer.

5. CONCLUSION

In this Account, we have presented various functions and applications of capsules constructed by subcomponent self-assembly. The diverse three-dimensional structures of the capsules impart varied host-guest properties with subtle differences in the structure of subcomponents sometimes resulting in incommensurate effects on the guest binding behavior of the resulting hosts. Fundamental investigations into simple host-guest systems involving neutral or anionic guests binding to a single host have paved the way to new functions in the contexts of guest protection, catalysis, chemical purification and interfacing with biological systems, providing new means to address industrial, environmental and biomedical problems using supramolecular strategies. The dynamic nature of subcomponent self-assembly has enabled the development of multi-cage systems involving signals to be passed between different hosts and guests, allowing complex functional behavior in response to stimuli. These systems represent a step towards mimicking the functions expressed by complex biological systems of molecules organized into networks, which collectively express functions.

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Notes

The authors declare no competing financial interest.

Biographical Information

Dawei Zhang undertook his undergraduate studies at the Northeastern University in China (2007-2011). He carried out a co-sponsored PhD program between East China Normal University (2011-

2013) and École Normale Supérieure de Lyon (2013-2017) under the supervision of Prof. Guohua Gao and Prof. Alexandre Martinez, respectively, focusing on molecular recognition and supramolecular catalysis with covalent macrocycles or cages. He began his post-doctoral research on metal-organic capsules in the group of Jonathan Nitschke at the University of Cambridge in July 2017, and took up a Herchel Smith Post-doctoral Research Fellowship in October 2017.

Tanya K. Ronson received a Bachelor of Science with Honours from the University of Otago in 2003. She completed a PhD in metallo-supramolecular chemistry in 2006 under the supervision of Prof. Michael Ward at the University of Sheffield and then went on to carry out post-doctoral research with Prof. Michaele Hardie at the University of Leeds. Since 2011 she has been a post-doctoral research fellow in the group of Jonathan Nitschke at the University of Cambridge focusing on the synthesis and host–guest behavior of aromatic-paneled metal-organic cages.

Jonathan R. Nitschke was born in Syracuse, New York, USA. He received his bachelor's degree from Williams College in 1995 and his doctorate from the University of California, Berkeley in 2001 under the supervision of T. Don Tilley. He then undertook postdoctoral studies with Jean-Marie Lehn in Strasbourg under the auspices of a US NSF fellowship, and in 2003 he started his independent research career as a *Maître-assistant* (fixed-term independent PI) in the Organic Chemistry Department of the University of Geneva. In 2007 he was appointed University Lecturer at Cambridge, where he now holds the position of Professor. His research investigates the self-assembly of complex, functional structures from simple molecular precursors and metal ions.

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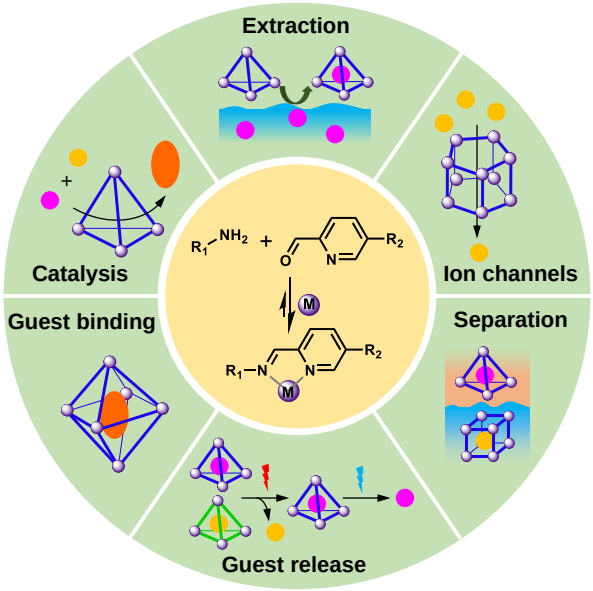
Extraction
Ion channels
Separation
Guest release
Guest binding
Catalysis
NH2
R1
R2
O
N
M